Substance Abuse Among Women: Familial Factors and Comorbidity

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INTRODUCTION

There is a substantial body of literature on the role of familial factors in substance abuse; however, most current knowledge has been derived from studies that focus exclusively on alcoholism. In general, there is a relative paucity of literature on familial factors and other drug abuse. In addition, there is a dearth of evidence about the role of genetic factors in substance abuse among females because of the small numbers of women in most studies. This chapter (1) reviews epidemiologic evidence regarding sex differences in the prevalence of substance abuse, (2) examines whether these sex differences can be attributed to genetic factors, and (3) investigates the role of psychiatric comorbidity in sex differences in substance use disorders.

SEX DIFFERENCES IN THE EPIDEMIOLOGY OF SUBSTANCE ABUSE AND DEPENDENCE

Epidemiologic Studies

Several large-scale community-based studies of psychiatric disorders have been conducted in the United States over the past several decades. The Epidemiologic Catchment Area (ECA) Study (Robins and Regier 1991; Kessler et al. 1996) was a landmark investigation conducted during the early 1980s with the chief goal of estimating the prevalence of psychiatric disorders in five large regions in the United States. The National Comorbidity Survey (NCS) (Kessler et al. 1996), which followed the ECA by almost a decade, is based on a national, stratified, multistage area probability sample of noninstitutionalized adults (Kessler et al. 1994). The major differences between these two surveys are the national sampling frame of the NCS compared with the five-site design of the ECA; the use of the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (*DSM-III-R*) (American Psychiatric Association 1987) in the NCS rather than the *Diagnostic and*

Statistical Manual of Mental Disorders, Third Edition (*DSM-III*) (American Psychiatric Association 1980); more indepth probing by the NCS of psychiatric symptoms endorsed by the subjects; and a more sensitive probing method used to reduce recall errors in the NCS.

Table 1 presents the rates of substance use disorders by sex for both the ECA and NCS. In general, the rates of substance use disorders were higher among males than females (Anthony and Helzer 1991; Helzer et al. 1991; Kessler et al. 1994); however, the overall rates of all disorders were substantially higher in the NCS study. These studies reveal that although drug abuse and dependence are more common among men than among women, the sex ratio for drug abuse is closer to equal than that for alcoholism (Regier et al. 1990*b*; Warner et al. 1995). There is an average twofold to threefold excess of males relative to females with alcoholism compared with a 1.5-fold to twofold excess of males with abuse of other drugs. This difference in the sex ratio is particularly pronounced for drug dependence, for which there is a nearly equal sex ratio. Thus, there appears to be an inverse relationship between the extent of availability of substances and the decrease in the severity of the threshold of problematic substance use and sex differences in substance use disorders; that is, the male excess is greatest for use of widely available substances and least for dependence on "harder" drugs (e.g., cocaine or opioids).

The age-specific distribution of drug dependence also differs between men and women. Epidemiologic data have demonstrated that there is a greater decrement in the cumulative probability of the development of

TABLE 1. *Rates per 100 of substance use disorders, by sex*

	Epidemiologic Catchment Area Study		National Comorbidity Survey	
	Males	Females	Males	Females
Alcohol abuse	10.3	1.8	12.5	6.4
Alcohol dependence	2.7	0.5	20.1	8.2
Alcohol abuse and dependence	10.9	2.3	—	—
Other drug abuse	3.8	2.1	5.4	3.5
Other drug dependence	4.5	2.6	9.2	5.9
Other drug abuse and dependence	—	—	35.4	17.9

drug dependence among males than among females who use drugs, thereby indicating that the risk period for women is longer than for men (Warner et al. 1995). This has important implications for treatment and prevention in women; although there is a relatively equal age at onset of drug dependence for both sexes, the risk period for that onset extends to midlife in women.

SEX DIFFERENCES IN FAMILY AND GENETIC STUDIES OF SUBSTANCE ABUSE

Background

The familial aggregation of alcoholism has been well established (for comprehensive reviews, see Merikangas and Gelernter [1990] and McGue [1994, pp. 1-40]). On average, controlled family studies of probands with alcoholism reveal an approximate threefold increased risk of alcoholism and a twofold increased risk of other drug abuse among the relatives of probands with alcoholism compared with those of controls. Several family studies that used information obtained from the proband (Hill et al. 1977; Meller et al. 1988) and uncontrolled family studies with direct interviews or questionnaires used to assess relatives (Scherer 1973; Annis 1974; Croughan 1985, pp. 18-33; Mirin et al. 1991; Rounsaville et al. 1991*a*; Gordon 1994) suggest that there is a strong degree of familial clustering of drug disorders as well. However, much of the evidence on the familial aggregation of drug abuse is taken from family studies that have not used contemporary family study methods, including systematic ascertainment of probands, independent enumeration and blind assessment of relatives, application of standardized diagnostic methods, and a control or comparison group with comparable information on relatives.

To date, there are only two family studies of drug abusers in which relatives were interviewed directly (Mirin et al. 1991; Rounsaville et al. 1991*a*) and only one family study with a non-drug-abusing control group (Rounsaville et al. 1991*a*).

Sex Differences in the Familial Aggregation of Substance Abuse

Most family and genetic studies of alcoholism have focused exclusively on males. However, several family, twin, and adoption studies

have demonstrated sex-specific patterns of transmission of alcoholism (Cloninger et al. 1978; Hill and Smith 1991). One review of evidence for genetic mediation of alcoholism in women concluded that genetic factors appear to operate similarly in males and females. However, the authors underscore the need for studies with sufficient numbers of female probands (Hill and Smith 1991).

Only two published studies have investigated twin concordance for drug abuse or dependence in a large series of twins (Pickens et al. 1991; Jang et al. 1995); however, some studies have examined twin concordance for patterns of alcohol use among women (Heath et al. 1989). Although concordance rates are greater in female monozygotic pairs than in dizygotic pairs, few studies have had a sufficient number of female twin pairs to yield conclusive evidence regarding the heritability of drug abuse. Pickens and associates (1991) found that both male and female monozygotic twin pairs had a 1.5-fold increased risk of drug abuse compared with dizygotic pairs, but the heritability of drug abuse was significant only for males, possibly because of the low number of female pairs with drug abuse. Sex differences in the components of genetic and environmental factors also emerged; the concordance for males could be attributed to both shared genes and environmental factors, whereas for females, the majority of variance was attributable to the unique environmental experiences of individual twins. Thus, no evidence for direct influence of genes on the development of drug dependence in women has been established. Evidence from adoption studies has been somewhat conflicting in terms of sex differences. Whereas Grove and colleagues (1990) reported greater heritability of drug abuse among males, Cadoret and coworkers (1995, 1996) reported equivalent genetic pathways underlying substance abuse among males and females.

In addition to providing evidence about the possible role of transmissible genetic factors, family studies can be used to investigate sources of a sex difference in the prevalence of a particular disorder. If the sex difference can be attributed to genetic factors, familial aggregation data should reveal an increased risk of this condition among relatives of the less frequently affected sex (Merikangas et al. 1985). That is, if there is greater loading for the genetic factors that contribute to the expression of a particular disorder in one sex, relatives of an index person also should manifest these factors at a much greater frequency than those of the more frequently affected sex because the threshold is lower. Family

study data have been used to investigate sex differences in birth defects, pyloric stenosis, and stuttering (Falconer 1965; Kidd and Spence 1976; Pauls and Kidd 1981, pp. 331-362). A sex-specific transmission model was first applied to alcoholism by Cloninger and colleagues (1978). This chapter applies family study data to investigate sex differences in the transmission of substance abuse.

SEX DIFFERENCES IN COMORBIDITY OF SUBSTANCE ABUSE AND PSYCHIATRIC DISORDERS

The term "comorbidity," introduced by Feinstein (1970), refers to the presence of any additional coexisting ailment in a patient with a particular index (i.e., primary) disease. Nonrandom co-occurrence of two conditions may be attributable to several methodologic artifacts, including samples selected from clinical settings that are nonrepresentative of persons with the index disease in the general population (i.e., "Berkson's Paradox") (Berkson 1946); assessment bias, in which the co-occurrence of two conditions is an artifact of overlap in the diagnostic criteria or in the assessments used to ascertain the criteria; and the lack of an appropriate comparison or control group with which to account for factors that confound the association between the two conditions.

Clinical Studies

The prevalence of psychiatric illness among people in treatment for substance abuse is high (Penick et al. 1988; Rounsaville et al. 1991*a*). Several studies have found high rates of comorbidity between alcoholism and anxiety disorders (Woodruff et al. 1972; Ross et al. 1988; Regier et al. 1990*a*, 1990*b*; Schuckit et al. 1990), affective disorders (Merikangas and Gelernter 1990), and antisocial personality disorder (Woodruff et al. 1979, pp. 14-27; Powell et al. 1982; Schuckit 1983*a*, 1983*b*, 1983*c*; Robins et al. 1988, pp. 15-30) among adults in treatment for alcoholism. Similarly, substance abuse and dependence in general have been shown to be strongly comorbid with major depression, bipolar disorder, antisocial personality disorder, and anxiety disorders in samples of clinically treated adults addicted to cocaine and opioids (Chitwood and Morningstar 1985; Gawin and Kleber 1986; Griffin and Friedman 1986; Weiss et al. 1988; Rounsaville et al. 1991*a*, 1991*b*; Luthar and Rounsaville 1993).

Relatively few studies have focused specifically on the comorbidity between substance use disorders and psychopathology among females. In a sample of 100 treatment-seeking people who abused substances, Brady and colleagues (1993) reported more overall comorbid diagnoses among females than among males. This elevation in rates was particularly evident among women with anxiety disorders, although the rates were not substantially different from those of population-based norms. In contrast, males in this sample showed higher rates of affective disorders. There were no differences by sex for the Axis II disorders (American Psychiatric Association 1987). Likewise, Hesselbrock and coworkers (1985) reported increased rates of panic, depression, and phobic disorders among females who were in treatment for alcoholism.

Epidemiologic Studies

In both the ECA and NCS, substantial comorbidity was observed between many of the *DSM-III* (American Psychiatric Association 1980) and *DSM-III-R* (American Psychiatric Association 1987) Axis I psychiatric disorders and both alcoholism and other drug abuse. The ECA revealed that more than 50 percent of people who abused substances also had at least one mental disorder, with lifetime prevalence ratios of 28 percent for anxiety disorders, 26 percent for affective disorders, 18 percent for antisocial personality disorder, and 7 percent for schizophrenia (Regier et al. 1990*a*).

An examination of the prevalence rates of disorders comorbid with substance use disorders reveals that both substance abuse and dependence are highly comorbid with antisocial personality disorder, anxiety disorders, and affective disorders, irrespective of sex (Regier et al. 1990*a*, 1990*b*; Anthony and Helzer 1991; Helzer et al. 1991; Kessler et al. 1996). Table 2 presents the prevalence ratios among males and females for a number of *DSM-III* diagnoses comorbid with substance use disorders from the ECA. Although the rates of all disorders among females with alcoholism or other drug abuse are greater than those for population base rates, the rates are particularly elevated for antisocial personality disorder, mania, and schizophrenia. That is, when a female is alcoholic or drug dependent, she is more likely than a male to exhibit concomitant antisocial personality disorder (Helzer and Pryzbeck 1988; Helzer et al. 1991). Helzer and Pryzbeck (1988) also have reported a sex differential in which alcoholic females were far more likely than

TABLE 2. *Comorbidity of substance abuse or dependence and other psychiatric disorders: Prevalence ratios from the Epidemiologic Catchment Area Study*

	Females		Males	
	Alcohol Abuse/ Dependence	Other Drug Abuse/ Dependence	Alcohol Abuse/ Dependence	Other Drug Abuse/ Dependence
Antisocial	29.6*	26.6*	12.0	7.3
Alcoholism	—	9.0*	—	2.9
Other drug abuse/ dependence	8.8*	—	4.8	—
Major depression	2.7	3.6	2.4	4.9
Mania	9.3	11.1	6.5	11.3
Dysthymia	2.2	3.1	2.5	5.1
Panic	4.4	2.9	4.2	4.1
Phobias	2.1	1.9	1.8	2.4
Obsessive compulsive disorder	2.1	3.5	3.0	3.6
Schizophrenia	5.6	6.4	4.6	6.2

*Significantly greater than comorbidity rates among males

alcoholic males to have a diagnosis of major depression when compared with population rates of the United States at large. Furthermore, females with alcoholism were more likely to report that onset of depression followed that of alcoholism, whereas males with alcoholism were more likely to report that the onset of depression preceded that of alcoholism. The high magnitude of comorbidity between substance abuse and psychopathology in this large-scale community survey suggests that the frequent co-occurrence of these conditions reported from clinical samples is not simply an artifact of sampling bias.

Familial and Genetic Studies

Although much research has addressed the familial patterns of alcoholism and other drug abuse, the familial patterns of comorbidity among people who abuse substances have received scant attention, particularly with regard to sex differences. Application of the family study paradigm to elucidate mechanisms for comorbidity requires probands selected for the presence or absence of the comorbid disorder under study as well as suitable controls that use ascertainment and

assessment methods comparable to those used with the probands. The lack of consistent methodology in previous family studies of drug abuse limits their ability to address adequately the cosegregation of substance use disorders and psychopathology.

Several studies have used family history data to examine the etiologic overlap between alcoholism and other drug abuse. Hill and colleagues (1977) concluded that alcoholism and opioid abuse were transmitted independently; likewise, Meller and coworkers (1988) demonstrated specificity of transmission of alcoholism and other drug abuse among relatives of probands with substance abuse.

Numerous family history studies and systematic family studies of substance abusers in treatment settings (Hill et al. 1977; Croughan 1985, pp. 18-33; Gfroerer 1987; Meller et al. 1988; Mirin et al. 1988, 1991; Rounsaville et al. 1991*a*) have reported a significantly higher risk for both alcoholism and other drug abuse among relatives of people who abuse substances than among the general population. Rounsaville and colleagues (1991*a*) reported a sex difference in comorbidity among relatives of people who abuse substances. That is, there were higher rates of alcoholism, other drug abuse, and antisocial personality disorder among the male relatives of people addicted to opioids, whereas anxiety and affective disorder rates were elevated among the female relatives of people who abused substances. However, these findings are suggestive at best because of the lack of adequate evidence from family studies that use contemporary family study methodology, particularly control groups, in investigating familial patterns of drug abuse.

Recent family studies by Merikangas and colleagues (1994), Maier (1993), and Maier and Merikangas (1996) investigated the familial patterns of comorbidity between the affective disorders, anxiety disorders, and alcoholism. On the basis of an elevated risk of alcoholism among the relatives of probands with pure panic disorder, patterns of cosegregation of alcoholism, depression, and anxiety disorders among relatives of probands—with each of these conditions compared with controls—suggested some degree of shared susceptibility factors for alcoholism, panic, and depression. These results were confirmed in a recent uncontrolled family study of anxiety disorders that also suggested an etiologic relationship between anxiety disorders and substance abuse (Skre et al. 1994).

Aside from their traditional goal of discriminating between the roles of genetic and environmental factors and their interaction in the development of a disorder, adoption studies also have been informative in examining the links between substance abuse and psychopathology. The classic adoption studies of Cadoret and coworkers (Cadoret 1992, pp. 99-113; Cadoret et al. 1985) identified two major biologic or genetic pathways to the development of drug abuse in adoptees: One is driven by substance abuse in the biologic parent and is limited to drug abuse and dependence in the adoptee, and the other appears to be an expression of underlying aggressivity and to be related to criminality in the biologic parent (Cadoret et al. 1995). Recently, these researchers extended their findings to include a female sample of adoptees, who over the longitudinal course were found to manifest a genetic pathway similar to that of males: A biologic parent with antisocial personality disorder was associated with the development in the offspring of conduct problems in adolescence and aggressivity and substance abuse problems in adulthood (Cadoret et al. 1996).

YALE FAMILY STUDY

The remainder of this chapter presents the results of the authors' large-scale family study, which was specifically designed to examine the mechanisms for comorbidity among alcoholism, other drug abuse, and anxiety disorders, as well as sex differences in the transmission of substance abuse/dependence. Comorbidity and cotransmission of marijuana abuse or dependence and anxiety disorders were examined to investigate the nature of the relationship between these disorders. The risk of marijuana abuse or dependence was assessed among 1,215 adult first-degree relatives of 260 probands with marijuana abuse or dependence, alcohol abuse or dependence, and anxiety disorders and among normal controls. These probands were ascertained from either treatment settings or the community through a random digit dialing procedure. The methods of this study are detailed elsewhere (Merikangas et al. 1996, in press). Preliminary findings revealed a lack of shared underlying factors in the familial transmission of alcoholism and other drug abuse.

The sample consisted of three groups: (1) 36 probands with marijuana or sedative abuse or dependence, (2) 88 probands with alcohol

abuse or dependence, and (3) a psychiatric control group composed of 76 subjects with anxiety disorders and 60 subjects without *DSM-III-R* diagnoses. The probands are described in table 3. Although equal proportions of male and female probands were in the marijuana or sedative group, there were approximately twice as many males in the alcohol group and twice as many females in the control group. There were no differences among the three groups with respect to age; however, a larger proportion of probands in the alcohol and marijuana/sedative groups were divorced and were from a lower socioeconomic group. Similarly, both the alcohol and the marijuana/sedative groups had significantly lower global assessment of functioning scores compared with the control group. The number of relatives within each proband group is noted at the bottom of the table.

A diagnostic description of the probands revealed that, with respect to anxiety disorders, panic with agoraphobia was higher in both the marijuana/sedative and control groups than in the alcohol group. In contrast, agoraphobia without panic was higher in the alcohol group than in the marijuana/sedative and control groups. All the affective disorders (major depression, bipolar disorder, and dysthymia) were significantly higher in the alcohol and marijuana/sedative groups than in the control group. The majority of marijuana/sedative abuse/dependence probands also had a lifetime history of alcohol abuse/dependence. There were significant differences between the groups with respect to

TABLE 3. *Yale Family Study of specificity of transmission of substance use disorders: Description of the sample*

	Diagnoses of Probands		
Probands	Marijuana or Sedative Abuse or Dependence (N=36)	Alcohol Abuse or Dependence (N=88)	Psychiatric Control Group (N=136)
Male (percent)	58	70	34
Age (mean)	36	40	40
Socioeconomic status (percent Hollingshead>3)	94	81	57
Married (percent)	64	57	88
Global assessment of functioning (mean)	61	62	76
Number of relatives	185	414	619

rates of current diagnoses of marijuana/sedative abuse or dependence and alcohol abuse/dependence; however, there were no differences in the rates of current anxiety disorders. Antisocial personality disorder was significantly higher in both the marijuana/sedative and alcohol groups than in the control group.

Table 4 presents the rates of substance use disorders among relatives of probands according to the sex of the relative. There was specificity of both alcohol abuse/dependence and marijuana/sedative disorders, with a significant increase in the rates of marijuana/sedative abuse/dependence among both male and female relatives of probands with marijuana/sedative abuse/dependence. There were sex differences in the prevalence rates of alcohol disorders, particularly alcohol dependence, with the rate for males twice that for females. Although males had higher rates of marijuana/sedative disorders, the differences by sex for dependence for marijuana/sedative disorders were not significant. Whereas relatives of probands with marijuana/sedative dependence had elevated rates of alcohol abuse/dependence, relatives of probands with alcohol abuse/dependence did not have significantly elevated rates of marijuana/sedative disorders. This finding suggests some degree of specificity in the familial aggregation of marijuana/sedative disorders. Across all proband

TABLE 4. *Yale Family Study of specificity of transmission of substance use disorders: Rates per 100 of substance use disorders in relatives*

	Diagnoses of Probands					
	Marijuana or Sedative Drug Disorders (N=185)		Alcohol Abuse or Dependence (N=414)		Psychiatric Control Group (N=619)	
Diagnosis in Relatives	Male	Female	Male	Female	Male	Female
Alcohol abuse	7.5	12.0	15.6	9.1	12.9	6.5
Alcohol dependence	41.9	9.8	34.1	13.9	17.1	5.5
Alcohol abuse and dependence	48.4	21.7	48.8	22.5	28.7	11.3
Marijuana/sedative abuse	16.1	7.6	10.2	2.9	4.8	2.3
Marijuana/sedative dependence	11.8	8.7	3.9	2.9	3.6	2.3
Marijuana/sedative abuse and dependence	22.6	15.2	13.7	5.3	7.4	4.2

groups, the rates of alcohol dependence among male and female relatives were much higher than those of alcohol abuse. As was observed with alcohol abuse, increased rates of alcohol dependence were observed among both the male and female relatives of probands with marijuana/sedative abuse or dependence or with alcohol abuse/dependence. Essentially the same pattern of results was observed when examining the specificity of transmission of marijuana/sedative abuse or dependence among the relatives of probands with marijuana/sedative abuse or dependence. That is, increased rates of marijuana/sedative abuse and dependence were observed among the male and female relatives of probands with either marijuana/sedative or alcohol problems. However, in contrast to the findings with alcohol abuse and dependence, the increased rates of marijuana/sedative abuse and dependence were specific to the female relatives of probands with marijuana/sedative abuse or dependence and were not specific to alcohol abuse/dependence.

Table 5 presents the rates of marijuana/sedative abuse/dependence according to sex of the proband and sex of the relative. Consistent with previous epidemiologic and family genetic studies, there was a twofold risk of substance abuse or dependence among the male relatives of probands with substance abuse or dependence compared with their female proband relatives (40.5 v. 19.0 percent, respectively). In contrast, there were approximately equal rates of substance use disorders among the relatives of male and female probands with substance use disorders.

TABLE 5. *Yale Family Study of specificity of transmission of substance use disorders: Rates per 100 of marijuana/sedative abuse or dependence among relatives, by sex of proband and sex of relative*

	Marijuana/Sedative Abuse/Dependence		
Probands	Males	Female	Total
Relatives:			
Marijuana/sedative abuse or dependence			
Males (n=608)	40.1	40.8	40.5
Females (n=610)	15.9	22.0	19.0
Total (n=1,218)	28.2	31.3	29.7

Table 6 presents sex-specific comorbidity odds ratios (ORs) for marijuana/sedative abuse or dependence and psychiatric disorders among relatives. These odds ratios were adjusted for age, history of alcoholism, and interview status (sex also was controlled for in the total sample). A significant degree of comorbidity existed between alcoholism and marijuana/sedative abuse/dependence disorders, anxiety, affective disorders, and antisocial personality disorder. Although there were no aggregate sex differences in the patterns of comorbidity of marijuana/sedative abuse/dependence and other conditions reported in table 6, investigation of specific subtypes of these disorders revealed some sex differences in comorbidity. With respect to anxiety disorders, panic and marijuana/sedative abuse/dependence disorders were significantly comorbid among females (OR=3.2) but not among males (none of the only seven male cases of panic disorder had a comorbid drug use disorder). Generalized anxiety disorder was significantly associated with marijuana/sedative abuse/dependence disorders among both males and females, whereas there was no significant association between drug use disorder and either social phobia or agoraphobia. All affective subtypes were elevated among both the male and female relatives with alcohol and other drug use disorders.

TABLE 6. *Yale Family Study of specificity of transmission of substance use disorders: Comorbidity of psychiatric disorders among male and female relatives (adjusted for age and interview status)[a,b]—odds ratios (±95 percent confidence limits)*

Disorder	Marijuana/Sedative Abuse/Dependence Males	Marijuana/Sedative Abuse/Dependence Females	Total
Alcoholism	10.6 (5.2-21.5)*	9.9 (4.3-23.1)*	10.5 (6.0-18.4)*
Anxiety[c]	2.6 (1.2-5.2)†	2.0 (0.8-4.9)	2.4 (1.3-4.2)‡
Affective[d]	2.5 (1.3-4.9)‡	3.6 (1.4-9.1)‡	3.0 (1.7-5.2)*
Antisocial personality	5.1 (1.9-13.5)‡	11.1 (2.5-49.4)‡	6.0 (2.7-13.5)*

[a]For antisocial personality disorder, anxiety, and affective disorders, alcohol status was controlled for in analyses.

[b]For "total" analyses, the sex of relative also was controlled for.

[c]Includes panic, generalized social phobia.

[d]Includes bipolar disorder, major depression, dysthymia.

*p<0.001

†p<0.05

‡p<0.01

Table 7 presents the results of multivariate modeling of the association between drug use disorders among probands and relatives after controlling for comorbidity and demographic factors. The results reveal specificity of transmission of marijuana or sedative use disorder (OR=3.6, $p<0.001$). There was no evidence of cross-transmission involving proband alcohol dependence or anxiety disorders. With respect to comorbidity among relatives, anxiety disorders in general were associated with substance use disorders among male (OR=2.4, $p<0.05$) but not among female relatives, whereas the affective disorders were more strongly associated among females. Antisocial personality disorder was highly comorbid with substance use disorders among both male and female relatives.

TABLE 7. *Yale Family Study of specificity of transmission of substance use disorders: Comorbidity and cotransmission of marijuana/sedative abuse or dependence and comorbid disorders among probands and relatives*

	Drug Abuse/Dependence		
Disorders/Covariates	Males	Females	All
Disorders in probands			
Marijuana/sedative abuse or dependence v. none	4.0*	2.9†	3.6*
Alcohol dependence v. none	1.2	1.3	1.2
Anxiety, all	0.7	0.2‡	0.5‡
Affective, all	1.1	5.0§	1.4
Antisocial personality disorder	0.9	—	0.6
Disorders in relatives			
Alcohol dependence v. none	7.2*	3.8§	5.8*
Anxiety, all	2.4‡	1.4	2.0‡
Affective, all	2.1‡	5.0§	2.7§
Antisocial personality disorder	4.7§	11.6§	5.4*
Covariates for relatives			
Interview v. none	0.7	0.8	0.7
Age	0.9*	0.9§	0.9*
Female v. male	—	—	0.5‡
Covariates for probands			
Female v. male	1.3	1.5	1.4

*$p<0.001$
†$p<0.10$
‡$p<0.05$
§$p<0.01$

DISCUSSION

Explanations for the Differences by Sex in Drug Abuse or Dependence

Numerous possible explanations exist for the differences by sex observed in the prevalence rates of substance use and psychiatric disorders. The differences by sex in affective disorder have been studied extensively (Weissman and Klerman 1977). Possible methodologic explanations such as reporting bias in women, as well as differences by sex in biologic, genetic, and sociocultural factors, have been considered as the chief sources of the female preponderance of depression. In general, the evidence suggests that the sex differences in depression are not an artifact of sampling or an increased tendency to report depressive symptoms in women, nor do they appear to result from increased genetic loading in women (Merikangas et al. 1985). Thus, the most likely sources of the sex differences in depression are a combination of biologic (e.g., neuroendocrine-triggered changes in the neurochemical factors underlying depression), psychological (e.g., different cognitive styles of women), and sociocultural factors (e.g., social role factors).

Epidemiologic data cited in this chapter suggest that women have lower rates of drug abuse than men. Application of family study data to examine whether the sex differences in drug abuse can be attributed to more genetic loading in women than men, according to the model developed by Cloninger and colleagues (1978), revealed that genetic factors are not the likely source of sex differences in drug abuse. Therefore, other explanations need to be explored. A review by el-Guebaly (1995) suggests several possible explanations for sex differences in drug abuse, including sex-specific biologic mechanisms, psychological vulnerability, and sociocultural factors.

Although some studies reveal increased concordance rates between same-sex parent-child pairs (i.e., mother-daughter, father-son) (Annis 1974), systematic family studies do not reveal greater familial aggregation of substance abuse among the relatives of female substance abusers than among male substance abusers (Mirin et al. 1991; Rounsaville et al. 1991*b*). The lack of sex differences in transmission of drug abuse observed in the Yale Family Study confirms this suggestive evidence but is far more conclusive than the evidence from previous studies because of the inclusion of a control group in the study design. The lack of sex differences in familial aggregation of substance abuse suggests similar

underlying genetic factors in the etiology of drug disorders among men and women. Therefore, sex differences are most likely a manifestation of either biologic or psychosocial factors that serve as a protective influence in women or enhance the development of substance abuse among men. Such factors could operate at the level of exposure or in the transition between use and abuse.

Comorbidity: One Mechanism for Familial Transmission of Substance Abuse?

In addition to genetic factors underlying metabolism and biologic and psychological effects of drugs, psychiatric disorders may be one of the transmissible familial factors that elevates the risk of drug abuse among relatives of substance abusers, particularly among women.

Sex Differences in Patterns of Comorbidity of Substance Use Disorders and Psychopathology

In general, patterns of comorbidity of substance abuse and psychopathology are equivalent for men and women. However, studies of clinical samples have shown that comorbidity of affective disorders is more common among male substance abusers than population expectations and that comorbidity of both affective and anxiety disorders is greater among female cocaine abusers than rates of comorbidity in epidemiologic studies (Brady et al. 1993). Most clinical research has focused on comorbidity of drug abuse with other manifestations of externalizing disorders such as antisocial personality disorder and alcoholism. Far less attention has been addressed to the comorbidity between internalizing problems such as depression or anxiety and substance abuse. The results of several clinical and epidemiologic studies reveal that affective and anxiety disorders are strongly associated with drug abuse among both sexes (Helzer and Pryzbeck 1988; Regier et al. 1990*b*; Kessler et al. 1996).

Investigation of specific subtypes of internalizing disorders yields some interesting sex differences in the role of primary disorders underlying the development of substance abuse. Epidemiologic and clinical studies reveal that bipolar affective disorder has the greatest association with drug abuse of all disorders in general and with individual subtypes of affective disorder specifically (Regier et al. 1990*b*; Brady and Sonne 1995).

The results of the Yale Family Study suggest that comorbidity of bipolar affective illness and substance abuse appears to be particularly elevated among women. The phobic disorders, particularly social phobia, are the subtypes of anxiety most strongly associated with substance abuse (Amies et al. 1983; Kushner et al. 1990; Regier et al. 1990*b*; Merikangas and Angst 1995; Kessler et al. 1996). Although the results of the Yale Family Study reveal a strong association between phobic states and substance abuse, the phobic disorders appear to increase the risk of drug abuse specifically among men.

Familial Patterns of Substance Abuse And Comorbid Psychopathology

The results of family studies of probands with different primary drugs of abuse, including opiates, cocaine, and marijuana (Hill et al. 1977; Meller et al. 1988; Mirin et al. 1991; Rounsaville et al. 1991*b*), suggest that the familial transmission of alcoholism and other drug abuse is independent. Several of the family studies of drug abuse also have investigated the degree to which comorbid disorders among people who abuse substances are associated with drug use and psychiatric disorders among their relatives. In general, results suggest that substance abuse and comorbid disorders are transmitted independently among relatives. That is, rates of affective disorders, antisocial personality, and anxiety disorders are elevated among the relatives of probands with these comorbid disorders themselves (Mirin et al. 1991; Rounsaville et al. 1991*b*). The data from the Yale Family Study support these findings regarding the lack of evidence of cosegregation of psychiatric disorders and substance abuse. Thus, although substance abuse and comorbid disorders tend to co-occur in individuals, they do not represent alternative manifestations of the same underlying etiologic factors in families. Comorbid psychiatric disorders could either be a cause or a consequence of drug abuse.

Role of Comorbid Disorders in the Development of Substance Abuse

Studies of the order of onset of drug abuse and psychiatric disorders tend to reveal consistent patterns of association between the externalizing and internalizing disorders in general and the development of drug

use and abuse in particular. Use and abuse of drugs appear to be part of a generalized pattern of deviant behavior with little specificity in the choice of specific substance of abuse (Jessor and Jessor 1977). Females with conduct problems and antisocial behavior tend to exhibit patterns of substance use and abuse similar to those of men (Robins and Price 1991). Moreover, the role of externalizing disorders, particularly conduct problems and aggressivity, in precipitating the use and abuse of drugs appears to be equivalent among males and females. Cadoret and colleagues (1995, 1996) have shown that this is the major pathway through which genes exert their influence on the development of drug abuse among both men and women.

Role of Longitudinal Studies in Establishing Causal Mechanisms

Longitudinal studies are important for the elucidation of causal relationships between disorders, the identification of common risk factors and their sequelae, and the discovery of homogeneous subtypes that may vary according to the stability of patterns of expression across the longitudinal course. Longitudinal studies of children have focused primarily on boys where the sequelae of conduct and behavior problems have been examined (Loeber 1982). However, conduct disorder is also clearly evident among girls, and the disproportionate attention to boys may result in a sex bias in the diagnostic criteria for identifying girls (Zoccolillo and Rogers 1991).

Retrospective data suggest that the pathways toward substance abuse can vary by sex. Conduct problems among girls are directly associated with the subsequent development of depression or anxiety, followed by alcohol or other drug abuse that appears to result from self-medication for depression, whereas among boys there is a more direct link between early behavior problems and antisocial behavior coupled with substance abuse (Robins and Regier 1991). A latent class analysis of problem behavior among teenagers that used prospective data from the New Zealand birth cohort study revealed that female problem behavior was likely to begin with accelerated transition to adult hedonic behaviors, including early sexual activity and use of alcohol and other drugs, whereas males tended to manifest a more generalized pattern of antisocial behavior (Fergusson et al. 1994). These findings indicate a clear need for prospective studies of girls at high risk for behavior problems.

The other major pathway for the development of substance use disorders is through the association between substance use and internalizing disorders. Data from the Yale Family Study suggest that bipolar affective disorder and social phobia appear to be the chief subtypes of depression and anxiety that lead to the development of substance abuse. In contrast, although both panic disorder and major depression appear to be associated with substance abuse, they appear to have no systematic role in precipitating the use or abuse of alcohol or other drugs. Weiss and coworkers (1992) have described the importance of the role of drugs in treating the manifestations of psychiatric symptoms and disorders. Therefore, self-medication of the early manifestations of the affective dysregulation present in bipolar disorder or the social anxiety that underlies social phobia is a likely explanation for the strong degree of comorbidity between these two subtypes of affective and anxiety disorders and substance abuse. Thus, women with either of these conditions, or even those at high risk for their development by virtue of a positive family history, should be an important target group for prevention efforts.

The consistency of the patterns of comorbidity (e.g., depression, anxiety, antisocial personality disorder) among the various substance use disorders has important implications for the development of treatment strategies, particularly when the onset of the conditions predates the substance abuse. Early prevention and intervention strategies should prove efficacious if the target populations are identified before the onset of illness. Weisner and Schmidt (1992) and Anthenelli and Schuckit (1993, pp. 73-87) have shown that the course of disease and treatment outcome are more complicated for substance abuse with comorbidity than for uncomplicated substance abuse and that women may have a worse course than men.

SUMMARY

The complex problem of psychiatric comorbidity among substance abusers and the implications for treatment are poorly understood. Scant attention has been paid to the role of comorbidity in discriminating sex differences during the course of treatment for women. Additional work is needed, particularly on identifying the causes of sex differences in drug abuse. Although the results of the Yale Family Study demonstrate a lack of genetic factors in the etiology of the sex differences in drug abuse,

confirmation in other samples is necessary. The results of this study suggest that examining mechanisms of comorbidity through the use of family study methodology and longitudinal studies serves as an important stepping-stone toward understanding the causes of sex differences in substance abuse.

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